

V. TB and HIV/AIDS

A. Standards of Treatment and Management

The majority of TB treatment principles apply to persons with HIV/AIDS who require treatment for TB disease. The following points are either unique to co-infected patients or deserve emphasis.

1. Review all medications individual is taking and assess for potential drug interactions with TB medications
 - Concurrent administration of rifampin (RIF) with certain HIV medications (antiretroviral therapy) may require adjusting the dosage of both types of medications to reduce the risk of drug toxicity and/or development of drug resistance.
 - **All HIV/TB patients must have their treatment regimens reviewed by a state TB Medical Consultant.**
2. A recent (within three months) CD4 lab result must be obtained for all HIV/TB patients. Those with CD4 counts $<100/\text{mm}^3$ at the initiation of therapy who are being treated for TB disease with the usual rifamycin-containing regimen (e.g., rifampin or rifabutin), should receive a daily DOT regimen for the entire course of therapy **Do not switch to a twice weekly or thrice weekly regimen.**

This policy should be followed for all HIV/TB patients with CD4 counts <100 regardless of disease site or drug regimen if a rifamycin is part of the regimen. See CDC. Notice to Readers: Acquired Rifamycin Resistance in Persons with Advanced HIV Disease Being Treated for Active Tuberculosis with Intermittent Rifamycin-Based Regimens. MMWR 2002; 51 No. RR-10; 1-3 for further information
http://www.cdc.gov/tb/publications/guidelines/tb_hiv_drugs/recommendations01.htm

3. All HIV/TB patients need to be monitored closely for response to treatment and signs of treatment failure or relapse; if failure or relapse is suspected, assume rifamycin resistance until culture-confirmed otherwise. Treatment modification will require consultation with a state TB Medical Consultant.
4. Most TB drugs should be calculated according to mg/kg body weight. Calculate on the lower figure in the range and round up to the next available dose supplied by the manufacturer (**For dosage table, see Chapter IV**).
5. HIV-positive individuals treated with INH should receive Pyridoxine (B_6) 25 mg daily or 50 mg twice weekly on the same schedule as INH.
6. Ingestion of 9 months of INH within a 12-month time period or four months of rifampin within a six-month time period is considered adequate treatment of latent tuberculosis.
7. All TB patients should be counseled and tested for HIV and a recent (<3 month) CD4 count report obtained if HIV-positive.

B. TST in HIV/AIDS

1. Once HIV infection is diagnosed, all individuals are required by law (10A NCAC 41A .0202) to receive a tuberculin skin test.
2. Annual testing of persons with HIV/AIDS should be considered for those persons with a substantial risk of exposure to TB.
3. For those whose initial TST was negative and whose immune function has improved in response to antiviral therapy (i.e., CD4 level has increased to > 200), the TST should be repeated.
4. Reactions of \geq 5mm induration are considered positive.

C. HIV/AIDS Candidates for Treatment of LTBI

All of the following individuals should receive treatment for LTBI

1. HIV/AIDS reactors (\geq 5mm) who have not previously received treatment for latent TB infection.
2. HIV/AIDS recent close contacts to known or suspected infectious TB disease regardless of previous LTBI and regardless of TST result:
 - First evaluate for TB disease, with symptom screen and chest x-ray;
 - If chest x-ray is normal, initiate treatment for LTBI in accordance with regimens found under E. of this chapter; and
 - If chest x-ray is abnormal, consult physician.
3. HIV/AIDS individuals with fibrotic changes on chest x-rays consistent with prior TB who have received inadequate or no treatment (regardless of TST result); or individuals with chest x-rays suggestive of healed primary TB disease (i.e. calcified solitary pulmonary nodules, calcified hilar lymph nodes, and/or apical pleural scarring), regardless of TST results, and only after TB disease has been ruled out.

D. Chest X-rays for Treatment of LTBI

1. HIV/AIDS individuals \geq 5 years of age or older should receive a posterior-anterior chest x-ray.
2. HIV/AIDS individuals < 5 years of age should receive a posterior-anterior and lateral chest x-ray.
3. HIV/AIDS individuals with a previously documented positive TST and a negative chest x-ray should have a repeat x-ray only when symptoms for tuberculosis disease are present.

E. Latent TB Infection (LTBI) Treatment Regimens for HIV/AIDS Individuals

1. The preferred regimen for all adults and children who have HIV/AIDS who are on antiretroviral therapy is INH.
 - INH for nine months
 - Nine months is the required length of INH therapy for treating LTBI in adults or children known to be HIV-positive.
 - Dosage for INH is 300mg daily (270 doses) or 900mg twice-weekly DOPT (78 doses) for a total of nine months to be taken within a 12-month period of time, though use of twice-weekly INH by DOPT is generally not cost-effective and another regimen should be considered if possible.
 - INH for LTBI is contraindicated for individuals with active hepatitis or end-stage liver disease.
2. The preferred regimen for adults and children age ≥ 2 who have HIV/AIDS but are not on antiretroviral therapy is three months of weekly isoniazid-rifapentine (12 doses).
 - INH plus rifapentine for three months (12 doses)
 - Isoniazid plus rifapentine is administered once-weekly by directly-observed therapy for 12 weeks.
 - This regimen is the preferred treatment of LTBI in HIV-positive individuals who are not already on antiretroviral therapy (ART).
 - Regimen is contraindicated in HIV-positive individuals who are on ART. However, it can be safely used in most individuals who are not on ART.
 - Isoniazid is administered at a dose of 15 mg/kg (maximum 900 mg), plus 15 mg/kg of rifapentine (maximum 900 mg), given together once weekly for 12 weeks, taken within a 16 week period of time. Missed doses can still be administered up to 72 hours before the next dose.
 - Regimen is contraindicated for pregnant and breastfeeding women.
 - Rifapentine interacts with many other drugs. Please see Chapter VI of the NC TB Control Manual for a partial list of drugs that interact with rifapentine.
 - Health department nurses must enter all patients using this regimen into the North Carolina Disease Surveillance System (NCEDSS). The contact or LTBI wizard must be completed, including treatment completion information. All DOT doses must be entered into the DOT question package.
 - Note that 11 doses taken within 16 weeks is adequate for completion of INH/rifapentine treatment
3. Alternative regimen for adults with HIV/AIDS
 - RIF for four months –
 - This regimen is preferred in the following circumstances:
 - Intolerance to INH;
 - Individual is a close contact to INH-resistant, RIF-susceptible TB
 - Individual is high-risk for progression to active TB but is unlikely to adhere to a full nine-month course of INH;
 - Individual is at relatively high risk for hepatotoxicity from INH (e.g. excess alcohol use, concurrent hepatotoxic medication) ;
 - RIF interacts with many other medications, including oral contraceptives, warfarin and many antiretrovirals. The patient's medication regimen should

be carefully examined for potential medication interactions before prescribing RIF;

- Dosage for RIF is calculated according to body weight and rounded up to the next available dose. 10 mg/kg per day with a daily maximum of 600 mg;
 - Daily RIF (120 doses) should be given for a total of 4 months within a six-month period of time (**the 4-month regimen is only for those ≥ 15 years of age**);
 - RIF by itself may **not** be given on a twice-weekly schedule; and
 - If RIF cannot be used in this regimen, rifabutin may be substituted after consultation with TB nurse consultant or medical director
- RIF-PZA
 - Given the latest evidence of increased liver toxicity with this regimen RIF-PZA for treatment of latent TB infection is no longer recommended for routine use due to the unacceptable incidence of severe hepatitis resulting in hospitalization, liver transplantation and sometimes death.

4. Treatment of LTBI in pregnant women with HIV/AIDS

- a. Chest x-rays
 - Due to the risk of progressive and/or congenital TB, pregnant women should have a PA view of the chest (with appropriate shielding) as soon as possible, even during the first trimester of pregnancy if they have a positive TST.
- b. HIV-positive asymptomatic TST positive pregnant women with a negative chest x-ray should start INH preventive therapy as soon as possible; do not wait until after delivery.
- c. Treatment regimen
 - INH is recommended for treating LTBI during pregnancy regardless of antiretroviral therapy.
 - RIF is an acceptable alternative for pregnant women in the following circumstances:
 - Intolerance to INH;
 - The individual is a close contact to INH-resistant, RIF-susceptible TB;
 - The individual is high-risk for progression to active TB but is unlikely to adhere to a full nine-month course of INH; and
 - The individual is at relatively high risk for hepatotoxicity from INH (e.g. excess alcohol use, concurrent hepatotoxic medication)
 - RIF interacts with many other medications, including oral contraceptives, warfarin and many antiretrovirals. The patient's medication regimen should be carefully examined for potential medication interactions before prescribing RIF.
 - There are limited data for use of rifabutin (RBT) in pregnancy and it should be used with caution.

5. Monitoring

- a. Pre-treatment evaluation
 - Chest x-ray and symptom review to exclude active tuberculosis disease. If active disease is excluded, no further chest x-rays are recommended.
 - Obtain medical history including
 - previous adverse reaction to any TB drugs;
 - underlying liver disease;
 - previous INH-associated liver injury; and
 - current medications (for drug interactions, see Chapter VI)
 - Obtain a baseline liver profile on all HIV-positive individuals and respond to abnormalities the same as you would with individuals who are HIV-negative (see Chapter III).
 - If using rifampin or rifabutin, obtain a baseline CBC with platelets in addition to the liver profile. Respond to abnormalities as you would with HIV-negative individuals.
- b. Monitoring during treatment
 - Clinical assessment should be performed on all individuals taking treatment for LTBI, whether HIV/AIDS or HIV-negative at least monthly. Assess for:
 - adherence to the prescribed regimen; and
 - signs and symptoms of adverse drug reactions (for adverse reactions, see Chapter IV).
 - If individual is on a rifamycin, at each visit evaluate any changes in other medications for potential interactions with TB drugs.
 - Obtain hepatic function panel monthly.
 - Manage individuals with asymptomatic liver enzyme elevations, adverse reactions or hepatotoxicity the same as individuals who are HIV-negative (see Chapter III).

F. Tuberculosis Disease in HIV/AIDS Individuals

The treatment regimen in HIV/AIDS patients may involve different TB drugs, may require daily rather than intermittent dosing, and may require longer treatment duration.

1. Drugs used to treat TB in HIV/AIDS adults ≥ 15 yr.
 - a. If the patient is on antiretroviral therapy, the patient's TB treatment regimen should be reviewed with a state TB medical consultant. Further drug information is available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5302a6.htm>.
 - b. Individuals should receive the usual four-drug TB regimen (INH, RIF, PZA, and EMB) if they are not on antiretroviral therapy; if they are receiving only NRTI-class drugs (e.g., AZT, ddI, d4T) or efavirenz or nevirapine, they should also receive a rifampin-based regimen.

2. Individuals receiving any other antiretrovirals will need to have rifabutin (RBT) substituted for rifampin; this should be done in consultation with a state TB Medical Consultant.
 - a. Monitoring of patients taking rifabutin should include complete blood counts looking for neutropenia and thrombocytopenia; the patient should also be asked about uveitis (eye pain, visual changes).
 - b. Other drugs (clarithromycin and fluconazole, for example), can increase RBT levels and cause RBT toxicity.
3. When switching from a RIF based regimen to a RBT or non-rifamycin based regimen, **wait at least two weeks before initiating antiretroviral drugs so that the persistent effects of RIF do not interfere with the antiretroviral drug**
4. Serum drug levels should be considered for anyone with a CD4 count <100 and taking INH and/or RIF as part of the treatment regimen. Drug level testing is also indicated for anyone experiencing treatment failure or relapse within two years (**See Chapter IX for further information and specimen collection procedure**).
5. Intermittent versus daily treatment
 - a. HIV/AIDS patients whose CD4 count is >100mm³ are treated like HIV-negative individuals:
 - Give INH, RIF/RBT, PZA, EMB daily DOT for two weeks, then twice-weekly DOT for six weeks (**dose must be increased for intermittent therapy**);
 - Continue INH and RIF twice-weekly DOT for 18 weeks;
 - Discontinue EMB when initial culture results confirm fully susceptible organisms or initial culture is negative **and** individual is clinically improving; and
 - Discontinue PZA after eight weeks if culture results confirm fully susceptible organisms or initial culture returns negative **and** individual is clinically improving.
 - b. HIV/AIDS patients whose CD4 count is <100/mm³ at the initiation of therapy:
 - Should receive a daily DOT regimen for the entire course of therapy.
 - **Do not switch to a twice-weekly or thrice weekly regimen.**
 - This policy should be followed for all HIV/TB patients with CD4 counts <100 regardless of disease site or drug regimen if a rifamycin is part of the regimen. See CDC. Notice to Readers: Acquired Rifamycin Resistance in Persons with Advanced HIV Disease Being Treated for Active Tuberculosis with Intermittent Rifamycin-Based Regimens. MMWR 2002; 51 No. RR-10; 1-3 for further information.
- 6 Duration of treatment
 - a. The minimum duration of short-course rifampin or rifabutin-containing TB regimens is 26 weeks.

- b. If PZA is not started within the first two weeks of treatment and continued for the 1st 8 weeks of therapy, or if PZA is contraindicated, a minimum of nine months of INH and RIF is required and the first eight weeks of treatment must be administered daily by DOT.
- c. Treat for a minimum of four months after two sputum specimens convert to negative.
- d. If the patient has a cavity on initial x-ray **and** fails to convert two sputum specimens to negative within the first two months of treatment (based on the collection date) treatment must be extended for a total of nine months.

7. Regimens for Pregnant Women

- a. The only difference between treating HIV-positive and HIV-negative pregnant women is the use of PZA. The benefit of optimal treatment of TB disease in HIV-positive pregnant women outweighs the very small risk of PZA in pregnancy. Therefore, for HIV/AIDS and TB in pregnant women, follow the treatment recommendations in Section F.1.b above.
- b. SM is contraindicated for pregnant women.

8. Regimens for Infants and Children <15 yr.

- a. Individuals receiving regimens listed in Section F.1.b above can receive standard TB therapy:
 - Give INH, RIF, PZA, EMB daily DOT for two weeks, then twice-weekly DOT for six weeks (if CD4 count is >100).
 - Continue INH and RIF twice weekly DOT for 18 more weeks for a total of six months (**26 weeks**) of treatment.
 - Discontinue EMB when initial culture results confirm fully susceptible organisms to INH and RIF.
 - Discontinue PZA after eight weeks.
 - If susceptibility results are not done or unknown, give INH, RIF, PZA, EMB for eight weeks, followed by INH and RIF for 18 weeks.
 - Individuals too young to have visual acuity or red-green perception testing should receive EMB at a dosage of 15-mg/kg body weight, or EMB may be omitted at the discretion of the prescribing physician.
- b. Individuals receiving antiretroviral therapy where RIF is likely to interfere (e.g., PIs), call a NC TB Medical Consultant (see chapter IX- page 9, C. 1. d. for contact information).
- c. Infants and children with meningeal, bone/joint or miliary TB should receive a minimum of 12 months of therapy.

9. Regimens for Extrapulmonary TB Disease

- a. Individuals with TB disease at any site should have a chest x-ray and sputum specimens sent for smear/culture (if able to produce sputum).

- b. Adults with meningeal and bone/joint TB should be treated for a minimum of nine months, and many authorities recommend 12 months total. All other sites should be treated with the same drug regimens recommended for pulmonary TB.
10. Regimens for INH Resistance or Intolerance **(Consult with a State TB Medical Consultant)**
- a. Individuals on an initial regimen of INH, RIF, PZA, and EMB
- Discontinue INH; continue to treat with RIF, PZA, and EMB for a total of six months (26 weeks).
- b. Individuals on an initial regimen of INH, RIF, and EMB (no PZA)
- Discontinue INH; continue to treat with RIF and EMB.
 - The initial phase (the first eight weeks) must be administered by daily DOT).
 - Treat for a minimum of 12 months.
- c. Individuals on initial regimen of INH and RIF
- Repeat susceptibility studies;
 - Discontinue INH and continue RIF; and
 - Add PZA and EMB to the regimen if susceptible to these two drugs and then treat for six months (26 weeks) with the three drugs.
11. Regimen for RIF Resistance or Intolerance **(Consult with a State TB Medical Consultant)**
- a. Individuals on initial regimen of INH, RIF, PZA, and EMB
- Discontinue RIF.
 - Continue to treat with INH, PZA and EMB daily during the initial phase (the first eight weeks).
 - After the initial phase continue INH and EMB daily or intermittently
 - Treat for a total of 18 months (78 weeks).
12. Regimen for PZA Resistance or Intolerance **(Consult with a State TB Medical Consultant)**
- a. An "M.tuberculosis complex" isolate that is PZA resistant is likely to be M.bovis which is always PZA resistant. M.bovis can be acquired through unpasteurized milk or cheese, and, if the site of disease is pulmonary, can be spread to others.
- b. Individuals on an initial regimen of INH, RIF, PZA and EMB
- Discontinue PZA and EMB if sensitive to RIF and INH.
 - Treat with INH and RIF for nine months (39 weeks).
 - The initial phase (the first eight weeks) must be administered by daily DOT.
13. Multi-Drug Resistant TB (MDR-TB) **(Consult with a State TB Medical Consultant)**

- a. MDR-TB is resistant to both INH and RIF and may also be resistant to other first or second line drugs.
- b. Treatment must be individualized and prolonged based on medication history and susceptibility studies.
- c. Give at least three medications to which the organism is susceptible.
- d. The regimen should continue until sputum conversion is documented, followed by at least 12 months of treatment.
- e. Only daily therapy is used in the treatment of MDR-TB.
- f. **The NC TB Control Program should be consulted regarding the treatment regimen whenever treating an MDR-TB case.**

- 14. Monitoring is the same as for HIV-negative TB patients (see Chapter IV for monitoring guidelines).

G. Regimens for HIV-positive Contacts to Extrapulmonary TB Disease

- 1. Administer TST.
- 2. Consider ≥ 5 mm induration positive; evaluate, obtain chest x-ray, and treat in accordance with policy found in Section E.

H. Regimens for Contacts to INH Resistant TB disease, see Section E.2.b.

I. Regimens for Contacts to INH and RIF Resistant TB Disease (MDR) Regardless of Antiretroviral Therapy (see Chapter VII).